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receptor expressed by cells of the T-cell lineage, so that the complexes formed are taken up in cells which express the T-cell surface protein.

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**Remarks**

***I. Status of the Claims***

Applicants have amended claim 17. This amendment is supported in the specification at least at page 5, lines 7-10. The same amendment was previously made to claim 1, in the Response filed March 11, 1994. Therefore, entry of the amendment raises no new issues which must be considered by the Examiner. Entry of the amendment is respectfully requested as it places the application in better condition for allowance or appeal.

The Examiner has withdrawn from consideration claims 21-27, 30-31 and 35. Therefore, the active claims in this application are 1-20, 28-29, 32-34 and 36-40.

***II. Miscellaneous***

Applicants acknowledge with thanks, the Examiner's withdrawal of the § 102(b) rejection of claims 1, 6, 11, and 13-16.

### ***III. Obviousness-Type Double Patenting***

In the Office Action at paragraph 16, the Examiner maintained the rejection of claims 1-20, 28-29, 32-34 and 36-40 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 48, 50, 51 and 54 of copending application Serial No. 07/492,460 (herein the '460 application) in view Wu *et al.*, U.S. Patent No. 5,166,320 (AC1 - herein "Wu"), Knapp *et al.*, *Immunology Today* 10(8): 253-258 (1980) (herein "Knapp"), Goers *et al.*, U.S. Patent No. 4,867,973 (herein "Goers"), and Rossi *et al.*, U.S. Patent No. 5,114,019 (herein "Rossi"). Applicants respectfully traverse this rejection and incorporate by reference herein, reiterate and expand upon the response filed March 11, 1994. Applicants also wish to bring to the Examiner's attention that the '460 application issued as U.S. Patent No. 5,354,844 on October 11, 1994.

The Examiner raises three issues in rebuttal to Applicants' response of March 11, 1994, each of which will be addressed individually. First, it is alleged that,

one of ordinary skill in the art *would recognize* that where the introduction of nucleic acids, such as ribozymes, into T-cells is desired, one of ordinary skill would *necessarily* utilize proteins, such as gp120 or antibodies to T-cell proteins known to be capable of initiating endocytosis, in order to facilitate the introduction of DNA into the target cells.

(Office Action at page 2, lines 22-27.) (Emphasis added.) Applicants respectfully disagree.

Applicants submit that the Examiner has presented a conclusory argument based on hindsight reconstruction of the invention. The Examiner has presented no evidence based

upon the prior art why one "would recognize" that it would be "necessary" to utilize proteins such as gp120 or antibodies to T-cell proteins in the claimed invention. He has merely stated his own opinion that such is the case. Applicants assume that the knowledge to support the Examiner's contention is "personal knowledge," as such information is not present in the cited references. If this is indeed the case, Applicants respectfully request support of facts within the personal knowledge of the Examiner with an affidavit pursuant to 37 C.F.R. § 1.107 (b):

When a rejection in an application is based on facts within the personal knowledge of an employee of the Office, the data shall be as specific as possible, and the reference *must* be supported, when called for by the applicant, by the affidavit of such employee, and such affidavit shall be subject to contradiction or explanation by the affidavits of the applicant and other persons.

(Emphasis added.)

Further, and more seriously, the Examiner has failed to provide any reason whatsoever in the cited art why one of skill in the art would even want to introduce the nucleic acids into T-cells. Therefore, the Examiner is premising the rejection on the conclusion that one would have a reason to introduce nucleic acids such as ribozymes into T-cells. Thus, the rejection is based on conclusory arguments having no basis in the cited art.

Contrary to the Examiner's argument, the real issue is whether, based on claims 48, 50, 51 and 54 in the '460 application, in view of the art applied by the Examiner, would one in fact have a motivation and reasonable expectation of success of obtaining the invention of claims 1-20, 28-29, 32-34 and 36-40 in the present application. One would not.

Given the myriad of possibilities concerning what one might obtain by combining the art applied by the Examiner with the claims of the '460 application and the lack of any motivation to prepare the specifically claimed conjugates or complexes, the most likely possibility is that one would not obtain the claimed invention.

Next, the Examiner contends "it is the target cell that dictates what the targeting agent will be, this is a fact that would have been readily recognized by the routineer." Again the issue is, why would one pick such a target cell, *i.e.*, is there a suggestion within the art or within the claims of the '460 application which would make it obvious to use T-cells as the target cell in order to obtain the claimed invention. The answer is that there is no such suggestion in the art cited by the Examiner. Even assuming, *arguendo*, that a T-cell was selected as a target cell, merely selecting such a target cell would only define a broad scope of possible targeting agents. There would still be no suggestion concerning which specific group of targeting agents one would select.

Finally, the Examiner contends that "it was known in the art that CD4 and CD7 specific antibodies were capable of inducing endocytosis into T-cells (see Carriere, E. *et al.*)." Again, the Examiner has failed to indicate why the mere fact that CD4 and CD7 antibodies might be capable of inducing endocytosis into T-cells would lead to the claimed invention. Simply because such antibodies might induce endocytosis, there is nothing in the Carriere reference or in the claims of the '460 patent to motivate lead one to combine the claims with the cited art in order to obtain the claimed invention. The invention as a whole must be considered, not simply its individual parts. Therefore, based on the above

arguments, the obviousness-type double-patenting rejection is inappropriate and must be withdrawn.

***IV. Rejection of claims 1-20, 28-29, 32-34 and 36-40 under 35 U.S.C. § 101***

In the Office Action at paragraph 17, the Examiner maintained the rejection of claims 1-20, 28-29, 32-34 and 36-40 under 35 U.S.C. § 101 alleging that the invention as disclosed is inoperative and therefore lacks utility. Applicants respectfully traverse this rejection and incorporate by reference herein, reiterate and expand upon the response filed March 11, 1994.

Prior to addressing the specifics of the Examiner's rejection, Applicants wish to make clear that the claimed invention is drawn to a composition comprising either a protein-polycation conjugate, a protein-polycation/nucleic acid complex, a process for introducing nucleic acid(s) into cells or a pharmaceutical preparation containing active nucleic acids in the form of a complex. It is the above-referenced compositions or method for introducing nucleic acid into cells which must be considered when determining utility of the claimed invention. This the Examiner has not done.

Instead, the Examiner has unilaterally decided that *the utility* of the invention is solely that of a therapy for *in vivo* use. This is inapposite. Regardless of what the Examiner may suggest as possible uses for the claimed invention, the utility of the invention for § 101 purposes is established in the claimed invention's use as either a composition or a method for introducing nucleic acids into cells and therefore, *in vitro* applications are clearly sufficient to establish the utility. Furthermore, the Examiner has failed to show that the invention

would fail to operate, *i.e.*, as a composition or method of introducing nucleic acids into a cell *in vitro*.

If the Examiner continues to insist on a demonstration of *in vivo* utility, Applicants specifically request the Examiner to 1) establish the justification for such a requirement and 2) establish a basis for ignoring the additional utilities presented in the application. Applicants submit that the Examiner cannot ignore Applicants' disclosed utility and insist that the sole utility of the invention is as a therapy for *in vivo* use. In fact, to the contrary, Applicants need demonstrate only a minimal level of utility for the claimed invention in order to satisfy 35 U.S.C. § 101.

Applicants now address the specific points raised in the Examiner's rejection. First, at paragraph 17, line 4, Applicants note that the Examiner referring to the previously filed response, has asserted that "Applicant has used the sentence out of its context in an effort to support undisclosed utility for the invention." Applicants regret any incorrect impression that they may have given. Applicants still maintain, however, that at page 6, lines 12-13 of the Office Action of May 31, 1994, the Examiner recognizes the *in vitro* use of the invention by stating "while the treatment of T-cells could be undertaken *in vitro* (*ex vivo*) . . . " Regardless of whether this quotation refers to chloroquine or not, it still provides a recognition of an *in vitro* utility.

The Examiner next contends that "there has been no apparent contemplation of the use of the claimed invention in an *ex vivo* manner by Applicant." Applicants respectfully disagree.



Simply because the Applicants have referred to *in vivo* use of the claimed invention in the specification, this does not preclude its use in an *in vitro* setting. In fact, Applicants have demonstrated throughout the specification (at least at Examples 6-13) that the invention does in fact have utility *in vitro*, thereby meeting the criteria for minimal utility. Additionally, Applicants state in the specification at page 5, lines 6-10 that "[t]he aim of the present invention was to provide a system by means of which it would be possible to transport nucleic acids selectively into higher eukaryotic cells, particularly cells of T-cell lineage." Applicants fail to understand how such an aim of the invention precludes *in vitro* utility and again respectfully request the Examiner to explain why such an application fails to meet the utility standard under 35 U.S.C. § 101.

In any event, Applicants' claims are drawn, *inter alia*, to a composition comprising conjugates or complexes, not to "a method of treating a living patient." Therefore, while such conjugates or complexes certainly are expected to be useful *in vivo*, the plain meaning of the claim language, which must be used in interpreting the claim, refers merely to a composition. Applicants respectfully submit that the Examiner's assumption that the only utility of the claimed invention resides in *in vivo* therapies is based on a misreading of the present application. If the Examiner continues to maintain this rejection, Applicants respectfully request the Examiner to point out where in the specification Applicants have disclaimed the use of the claimed invention for other than *in vivo* therapy.

To summarize, as stated *supra*, the Examiner's rejection is totally incorrect because the claims are not drawn to "a method of treatment" but rather to a composition comprising either a protein-polycation conjugate or a protein-polycation/nucleic acid complex and a

method for introducing nucleic acids into cells. Such conjugates, complexes and methods have substantial *in vitro* utility. Therefore, the rejection should be withdrawn.

**V. *Objection to the Specification and Rejection of Claims 1-20, 28-29, 32-34 and 36-40 Under 35 U.S.C. § 112, First Paragraph***

At paragraphs 18 and 19, the Examiner maintained the objection to the specification and rejected claims 1-20, 28-29, 32-34 and 36-40 under 35 U.S.C. § 112, first paragraph as allegedly failing to provide an adequate written description of the invention, and allegedly failing to adequately teach how to make and/or use the invention, *i.e.*, failing to provide an enabling disclosure and failing to present the best mode contemplated by the Applicant for carrying out the invention *in vivo* in humans. Applicants respectfully traverse this rejection and incorporate herein by reference, reiterate and expand upon the response filed March 11, 1994.

Applicants once again draw the Examiner's attention to the fact that the claims are drawn to a composition comprising either a conjugate or a complex of protein-polycations or protein-polycation/nucleic acid or to a method of introducing nucleic acids into cells. It is enablement of this composition which must be addressed by the Examiner, *not* therapeutic use in humans.

The general issue of the *in vitro* operability of the claimed invention was addressed in the rebuttal of the § 101 rejection *supra*. Said rebuttal applies equally well to the § 112, first paragraph rejection. Further, the Examiner contends at paragraph 18(A), lines 6-7, that one particular embodiment is not believed operable for targeting nucleic acids into cells. This



conclusion is factually incorrect. In the specification at least at Example 13, on pages 40-41 and in Figure 7, Applicants report successful experiments showing incorporation of nucleic acids into cells using an antibody-protein A-polycation-nucleic acid complex. The Examiner's extensive hypothetical explanation as to why this would not work *in vivo* is irrelevant because Applicants have demonstrated that the complexes are in fact taken up into cells *in vitro*.

The Examiner also points out at paragraph 19, that "Applicant argues that the claims are not limited to the *in vivo* use of the invention. Applicant's specification specifically recites contemplated uses of the claimed invention as therapeutic modalities suitable for *in vivo* use." Once again, Applicants agree with the Examiner that the claimed invention has *in vivo* therapeutic modalities. Such modalities however, are irrelevant to the question of whether Applicants have adequately provided a written description of how to make and/or use the invention *in vitro* and whether the best mode contemplated by the Applicant has been set out.

Applicants have provided ample evidence showing how to make and/or use the protein polycation conjugates (specification pages 28-33) and showing *inter alia* that the protein-polycation complexes are in fact taken up by the cells (specification pages 33-41); and have further presented the best mode contemplated at the time of the filing of the application. Thus, the claims are based upon an enabling disclosure. Regardless of whether the specification specifically recites other contemplated uses, the issue for enablement is whether the specification provides sufficient information to enable one of skill in the art to make and use the claimed invention. Applicants have shown this to be the case. Therefore, the rejection of the claims under § 121, first paragraph is incorrect and should be withdrawn.

**VI. Rejections of Claims 17, 18, 36 and 38 under 35 U.S.C. § 102(b)**

At paragraph 21, the Examiner maintained the rejection of claims 17, 18, 36 and 38 under 35 U.S.C. § 102(b) as allegedly being anticipated by Wagner *et al. Proc. Natl. Acad. Sci. USA*, 87:3410-3414, 1990 (herein "Wagner").

Without acquiescing in the propriety of this rejection, however, and solely to expedite prosecution, Applicants have amended claim 17 to make it consistent with previously amended claim 1 which is not anticipated by Wagner. Therefore, amended claim 17 and those claims dependent on claim 17 (*i.e.*, claims 18, 36 and 38) are also no longer anticipated under § 102. Based on this amendment, the rejection of the claims under 35 U.S.C. § 102(b) is obviated and should be withdrawn.

**VII. Rejection of the Claims Under 35 U.S.C. § 103**

**A. Rejection of Claims 2-5, 7-10, 12, 37 and 39-40**

At paragraph 22, the Examiner maintained the rejection of claims 2-5, 7-10, 12, 37 and 39-40 under 35 U.S.C. § 103 as allegedly being unpatentable over Wu or Wagner *et al.* in view of Goers *et al.* (U.S. Patent No. 4,867,973 - herein "Goers") and Knapp *et al.*, *Immunology Today* 10:253-258, 1989 (herein "Knapp"). Applicants respectfully traverse this rejection, incorporate by reference herein, reiterate and expand upon the response filed March 11, 1994.

In the Office Action, the Examiner maintained his position that the combination of applied art renders the invention obvious. Applicants respectfully disagree. Before addressing the specific arguments, however, Applicants wish to reiterate that the Examiner has failed to establish a *prima facie* case of obviousness and has further failed to rebut effectively Applicants' arguments presented in the Response filed March 11, 1994.

The Examiner is in effect taking the following teachings and then attempting to combine them to arrive at the claimed invention without any suggestion to do so (in either the art or the body of knowledge which one of skill in the art might be expected to possess). the teachings are:

1. DNA bound to asialoglycoproteins and polycations (Wu); or
2. A transferrin-polycation conjugate, which is used in a process called transferrinfection (Wagner);

Either added to:

3. Therapeutic agents selected for their intended application (no mention of T cells) which are attached to antibodies or antibody fragments (Goers); and
4. Publically available T-cell-specific antibodies (Knapp).

The Examiner suggests that if we take the above teachings we will obtain the claimed invention. There is no suggestion, whatsoever, in the applied art to do so. Furthermore, the above four teachings can result in any of a myriad of possibilities, only one of which might conceivably lead to the claimed invention.

Applicants request the Examiner to explain why, given the myriad of possibilities

presented by each of the pieces of applied art and the lack of a suggestion to make the appropriate combination, one would obtain the claimed invention as opposed to something else altogether, *i.e.*, why would there be a motivation to combine the references and thereby have a reasonable expectation of success of obtaining the claimed invention?

Referring to Wu at page 13 of the previous Response, Applicants submitted that Wu presents nothing more than an invitation to try numerous different possible combinations. Applicants also submitted that the Examiner failed "to point out any reference in the art which would suggest to one of skill in the art, which variables are critical to change or where indications are found in the art leading to the appropriate changes necessary to obtain the claimed invention." Applicants contended that more must be presented by the Examiner to establish a *prima facie* case of obviousness. Simply saying that one of skill in the art would make such a change because a body of knowledge exists to which that individual might have access is not sufficient. There must be a clear reason why such a combination would have been obvious to one of ordinary skill in the art. The Examiner is specifically requested to rebut Applicants prior arguments and to lay out the factual basis in the art which supports his reasoning.

Simply because a single component of the claimed invention might be present in Wu is not sufficient to suggest its use in the claimed invention. It is impermissible for the Examiner to simply pick and choose individual parts of the claimed invention from the applied art and then attempt to plug them into the description of the claimed invention obtained from the specification. In this regard, Applicants reiterate the following argument from the Response filed March 11, 1994.

While the Examiner has picked and chosen individual characteristics of the claimed invention from each of the pieces of the applied art, he has failed to provide any argument concerning what the motivation (as found in the cited references) might be for combining Goers and Knapp with either Wu or Wagner. By picking and choosing individual characteristics of the invention and then trying to put these characteristics together to arrive at the claimed invention, the Examiner is taking each of the applied documents out of context. The Examiner appears to have found individual components of the claimed invention within the applied art, *i.e.* one piece of art may contain polycationic molecules, another piece of art may contain antibodies to a certain cell type, and still another piece of art might suggest the general use of therapeutic agents. While the Examiner might construe the art to suggest various components of the invention, nowhere is there a suggestion to combine these components. The Examiner's argument is analogous to saying that all of the chemicals necessary (e.g., A, B, C, D) to make a certain reagent are present in the prior art, therefore, it would be obvious to make a specific combination of A + B + C + D to achieve a result not suggested by the prior art. Clearly, such would not be the case. If one claimed a new reagent, there must be a good reason for combining the individual elements to form such a reagent. By analogy, the same situation exists for the claimed invention. Simply because the Examiner feels that individual components of the invention might be found in several different pieces of art, this does not in any way suggest the selective combination of these elements to achieve the claimed invention.

The Court of Appeals for the Federal Circuit clearly stated that:

What we stressed in *Kimberly Clarke*, and have repeated many times since, was that 35 U.S.C. § 103 requires analysis of a claimed invention as a whole: . . . *What must be found obvious to defeat the patent is the claimed composition.*

\* \* \*

Focusing on the obviousness of substitutions and differences, instead of the invention as a whole,

is a legally improper way to simplify the often difficult determination of obviousness.

*The Gillette Company v. S.C. Johnson & Son, Inc.*, 16 U.S.P.Q.2d 1923, 1927 (Fed. Cir. 1990).

While the cited references may recite some of the limitations of the instantly claimed invention, they do not suggest the selective combination of such characteristics to produce the protein-polycation conjugate capable of binding to a cell surface protein expressed by cells of the T-cell lineage. As such, the use of the applied art does not establish a *prima facie* basis for rejection under § 103.

Response of March 11, 1994 at pages 16-17.

Further, concerning Wagner, Applicants previously raised the issue that this piece of art refers to its delivery system as useful for "transferrinfection" and as such, clearly had *only* one contemplated use for such a system. Additionally, Wagner deliberately takes advantage of the ubiquitous expression on cells of the transferrin receptor. By employing transferrin as a targeting agent, a multiplicity of cell types are targeted. Contrary to this, the claimed invention specifically targets cells of the T-cell lineage. Applications for transfection using a polycation conjugate other than transferrin were not suggested, and nowhere was the possibility raised that antibodies or a protein capable of binding to a T-cell surface protein might replace transferrin in the conjugate. Applicants again request the Examiner to explain how this reference might be used in conjunction with the additional applied art to obtain the claimed invention. Simply because a transfection system might exist in the art, this does not suggest the alternate possibilities raised by the claimed invention.

The Examiner has also applied Carriere *et al.*, *Exp. Cell Res.* 182: 114-128 (1989) (herein, "Carriere") against the claimed invention. The Examiner is using this document to



support the contention that "antibodies which specifically directed materials into T cells were known in the art before the earliest priority date of Applicant." While Applicants acknowledge that Carriere discloses internalization of monoclonal antibody-gold-antigen complexes, this is distinct from the claimed invention. Further, the results of Carriere appear to direct the investigator solely to the use of ligand-gold conjugates. For example, see page 125, line 36, where it is stated that "[t]his validates the use of ligand-gold conjugates." Thus, there is no motivation provided by Carriere to use the antibodies could be used in other conjugates for other applications, *e.g.*, for transporting DNA into cells.

Finally, the Examiner has cited *In re Nilssen*, 7 U.S.P.Q.2d 1500 (Fed. Cir. 1988) for the proposition that "[w]hat would reasonably have been known and used by one of ordinary skill in the art need not be explicitly taught with regard to the claimed material." (Office Action at page 4, lines 32-34). Applicants have carefully reviewed *Nilssen* and have failed to find the recitation which the Examiner refers to. Therefore, Applicants respectfully request the Examiner to more clearly point out where the recitation is found in *Nilssen*.

*Both* a motivation to combine the references and a reasonable expectation of success of obtaining the claimed invention after combining the references are necessary to establish a *prima facie* case of obviousness. *In re Vaeck*, 20 U.S.P.Q. 1438, 1442, 1991. Neither can be found in the Examiner's combination of applied art. Therefore, based on the above arguments, the Examiner has failed to establish a *prima facie* case of obvious because he has failed to show any motivation to combine selectively the applied art or that following combination of the applied art there would be a reasonable expectation of obtaining the

claimed invention. As such, the rejection of claims 2-5, 7-10, 12, 37 and 39-40 is improper and must be withdrawn.

***B. Rejection of claims 28-29 and 32-34 under 35 U.S.C. § 103***

At paragraph 24, the Examiner has maintained the rejection of claims 28-29 and 32-34 under 35 U.S.C. § 103 as allegedly being unpatentable over Wu or Wagner, in view of Goers and Knapp and Haseloff *et al.*, *Nature* 334: 585-591, 1988 (Herein "Haseloff") or Rossi *et al.*, U.S. Patent No. 5,144,019 (herein "Rossi"). Applicants respectfully traverse this rejection and incorporate by reference herein, reiterate and expand upon, the response of March 11, 1994.

The Examiner sets forth the following purported teachings:

1. Synthetic ribozymes may be constructed to inactivate RNA of a particular gene (Haseloff).
2. HIV-I specific ribozymes were known before the time of the invention of the claimed subject matter (Rossi).

The Examiner alleges that based on the above teachings, in light of previously applied art, the claimed invention would have been obvious. Applicants respectfully disagree.

Applicants argued *supra* why Wu or Wagner in view of Goers and Knapp does not render obvious the claimed invention. These arguments are repeated and apply equally well to this rejection. Further, there is no motivation whatsoever to combine Haseloff or Rossi with Wu or Wagner and Haseloff and Rossi to achieve the invention of claims 28, 29 and 32-34.

Finally, the Examiner has applied an incorrect analysis to the issue of obviousness, stating that "[i]n view of the combined references, it is the conclusion of the Examiner that one could reasonably expect to arrive at the claimed invention . . . ." Rather, the Examiner should be asking: Is there a suggestion to combine selectively the applied art and further, upon combining the art, would one have a reasonable expectation of obtaining the claimed invention? The answer to this questions is no. Therefore, based on the above arguments, the rejection of claims 28-29 and 32-34 under 35 U.S.C. § 103 is inappropriate and must be withdrawn.

*C. Rejection of Claims 1, 3-7 and 11-16*

The Examiner has newly rejected claims 1, 3-7 and 11-16 under 35 U.S.C. § 103 as allegedly being unpatentable over Wu or Wagner in view of Goers and Knapp, and Carriere. Applicants respectfully traverse this rejection.

Applicants reiterate their arguments *supra* concerning Wu or Wagner in view of Goers and Knapp, as they relate to this rejection of the claimed invention. Additionally, the arguments used against these pieces of applied art in the Response filed March 11, 1994, are reiterated and incorporated herein by reference. As such, only Carriere *et al.* need be directly addressed. In any event, Carriere does not remedy the defects of the additionally applied art.

While Carriere discloses antigenic modulation induced by monoclonal antibodies adsorbed on gold particles, there is nothing in Carriere to indicate that such a phenomenon could be expected *a priori* to result in internalization of protein-polycation conjugates.

Carriere only directly addresses antibodies adsorbed on gold particles. Therefore, there would be no suggestion to take the antibodies of Carriere and attach them to a protein-polycation conjugate (even assuming that the additional applied art would result in such a complex - which Applicants do not admit). As such, this rejection of claims 1, 3-7 and 11-16 under § 103 is incorrect and must be withdrawn.

The foregoing amendment and remarks do not raise new issues or add new matter, and the Examiner is therefore respectfully requested to enter the amendment after Final. Furthermore, in view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account 19-0036. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX



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